REMARKS

Upon entry of this Amendment, claims 47-48, 50-54, 56-59, and 61-64 will be pending in the subject application. Claims 47-63 were pending. Claims 47-48, 50-54, 56-59, and 61-63 have been amended. Claims 49, 55 and 60 have been cancelled. Claim 64 has been added. Applicants have amended the claims without prejudice to their right to pursue any cancelled or deleted subject matter in one or more future patent applications.

Support for amended claims 47 and 58 may be may be found in the specification, *e.g.*, at original claims 3 and 9. Amended claim 48 may find support in the specification, *e.g.*, at original claim 3. Support for amended claims 50-53 may be may be found in the specification, *e.g.*, at original claims 4-7, respectively. Amended claims 54, 56 and 57 may find support in the specification, *e.g.*, at original claims 9, 10 and 11, respectively. Support for amended claim 59 may be found in the specification, *e.g.*, at original claims 3, 9 and 16. Amended claim 61 may find support in the specification, *e.g.*, at original claim 16. Amended claim 62 provides for more acceptable claim language, and may find support in original claim 62. Amended claim 63 may find support in the specification, *e.g.*, at original claim 16. New claim 64 may find support in the specification, *e.g.*, at page 3, lines 7-9, page 19, lines 26-29, and page 21, lines 29-32.

The amendments raise no issue of new matter.

A. Claims are definite

The United States Patent and Trademark Office ("the Office") rejected claims 49-53 and 55-57 under 35 USC §112(2) for allegedly being indefinite because:

1. it is deemed that claim 49 and 55 do not further limit the scope of the claim from which they each respectively depend; and
2. it is deemed that claims 50-53 and 56-57 are substantial duplicates within each set.

Applicants respectively traverse.

Because claims 49 and 55 have been cancelled, the rejection with respect to these claims is moot. However, with respect to claims 50-53 and 56-57, the claims within each set are not substantial duplicates, but rather particularly point out and distinctly claim the invention Applicants deem as theirs.

For example, amended claim 50 is directed to an alpha form of the crystalline hydrogen succinate salt of the compound of formula (I) ("Compound I"), whereas, amended claim 51 limits the alpha form of the crystalline hydrogen succinate salt of Compound I to one being characterized by an X-Ray powder diffraction spectrum as shown in Figure 1. Also, the expressions like, "alpha form of the crystalline hydrogen succinate salt of Compound I" are clearly discernible from the specification, *e.g.*, at page 6, lines 2-7. Then, amended claim 52 limits the X-Ray powder diffraction spectrum that characterizes the alpha form of the crystalline hydrogen succinate salt of Compound I as to one having the particular diffraction peaks recited therein and obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å). Meanwhile, amended claim 53 also characterizes the alpha form of the crystalline hydrogen succinate salt of Compound I, but by a different characterization means – namely, differential scanning calorimetry (DSC), rather than by X-Ray powder diffraction analysis.

Consequently, though each claim within the set of claims 50-53 is directed to the alpha form of the crystalline hydrogen succinate salt of Compound I, each claim particularly points out and distinctly claims the salt, with the dependent claims 51-53 using different, or in some instances more particular, solid state characterization data to further particularly points out and distinctly claim the salt. Applicants also respectfully submit that it is commonly accepted that a crystalline compound can be particularly pointed out and distinctly claimed by various characterization data through multiple claims, including as provided for in claims 50-53. *See e.g.*, US Patent Nos. 7,411,075, 7,381,737, and 7,326,708. Amended claims 50-53, therefore, are not indefinite.

Similarly, therefore, amended claims 57 and 57 particularly point out and distinctly claim the crystalline malonate salt of the present invention, and therefore, are not indefinite.

Accordingly, Applicants respectfully request the §112(2) rejection be reversed.

B. Claims are enabled

The Office rejected claims 54-57 under 35 USC §112(1) for allegedly not being enabling, apparently with respect to certain diseases and disorders as claimed in claims 58 and 60. *See* pages 2-3 of the Office Action. Applicants believe the Office meant the rejection for claims 59-

63 since the scope of these claims, and not claims 54-57 and 58, are directed to certain diseases and disorders. Under this belief, Applicants respectfully traverse the rejection.

Without conceding to the correctness of the Office's position and merely to advance prosecution, Applicants have amended claims 59, and 61-63, and cancelled claim 60. Applicants submit that amended claims 59, and 60-63, are enabled. For example, amended claim 59 now recites in relevant part:

> wherein the disease or disorder is selected from the group consisting of an anxiety disorder, depression, schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder and mania in bipolar disorder.

In fact, the Office acknowledged that the specification is enabled for these disorders. *See* page 2 of the Office Action; *see also*, page 3 of Office Action mailed May 13, 2008 in related case USSN 10/568,292. Consequently, claims 59 and 61-63 are enabled.

Applicants, therefore, respectfully request that the §112(1) rejection be reversed.

C. Claims are not obvious

The Office rejected claims 47-63 under 35 USC §103(a) for allegedly being obvious over the Bøgesø et al., *J. Med. Chem.* 1995, 38:4380-92 ("the Bøgesø reference") and EP 0 638 073 ("EP'073") in view of US Patent No. 4,443,449 ("US '449") ("the combined references"). Applicants traverse the rejection and respectfully request it be withdrawn.

For a claimed invention to be obvious, the teaching of a prior art reference or teachings of a combination of prior art references must be viewed in light of four factual inquiries:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

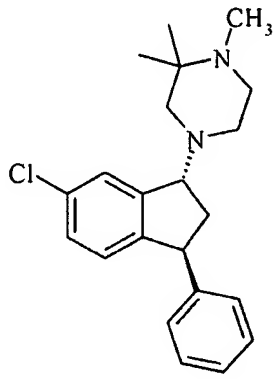
(d) evaluating evidence of secondary consideration.

See Graham v. John Deere, 383 U.S. I, 17-18, 148 USPQ 459,467 (1966). Whether the reference(s) teach, suggest or motivate one of ordinary skill in the art to combine the reference(s)

in a manner that achieves the claimed invention can be helpful in this determination for obviousness. *See KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007); *see also, e.g., Cordis Corp. v. Medtronic AVE Inc. 511 F.3d 1157 (Fed. Cir. 2008).*

In this instance, the Bøgesø reference fails to make the present invention obvious. For example, amended claim 47 recites:

> [a] crystalline succinate salt or a crystalline malonate salt of a compound of formula (I)



(I)

In contrast, the Bøgesø reference teaches the compound of formula (I) ("Compound I"), but as the fumarate and maleate salt forms and not as the succinate and malonate salt forms of the present invention, which the Office acknowledges. *See e.g.*, compound 38 in Table 5 of the Bøgesø reference; *see also*, Office Action, page 6. Moreover, the Bøgesø reference teaches that the (-) enantiomer of compound 38 are potent 5-HT_2 antagonists, potent D_1/D_2 antagonists, have high affinity for α_1 andrenoceptors, and do not induce catalepsy, while the (+) enantiomer is a potent inhibitor of DA and NE uptake. *See e.g.*, page 4386, text and Table 5. The Bøgesø reference further teaches that the racemic compound 38 and (-)38 enantiomer "have unusually potent effects" compared to the 4'-fluoro substituted derivative (compound 10), when it had been reported previously that such fluoro atom was necessary for a potent effect to be achieved. *See e.g.*, page 4385, text; *see also, e.g.*, Tables 3 and 5. In fact, the Bøgesø reference teaches that the (-)38 enantiomer and three other derivatives, "fulfill the goal of being a mixed antagonist" with potential as an atypical antipsychotic, and thus, would be selected for preclinical studies. *See e.g.*, page 4386, text.

Indeed, by its teaching that compound 38 (as a maleate salt) and its enantiomers (as fumarate salts), *e.g.*, have desirable potencies/affinities with respect to antipsychotic drugs, the Bøgesø reference teaches away from the present invention. The Bøgesø reference teaches away because, in its acknowledging these desirable qualities of compound 38 (as a maleate salt) and its enantiomers (as fumarate salts), not to mention at least the three other derivatives, the Bøgesø reference fails to provide an apparent reason for one of ordinary skill in the art to modify its teaching of the fumarate and/or maleate salts to achieve the succinate and malonate salts of amended claim 47.

The Bøgesø reference also teaches away because a particular goal of the Bøgesø reference "was to obtain new compounds with mixed profiles (D_1, D_2, 5-HT_2 and α_1) together with potent D1 activity." *See e.g.*, page 4381. This goal was achieved, and in fact, acknowledged with respect to compound 38 (as a maleate salt) and its enantiomers (as fumarate salts), as previously mentioned. *See e.g.*, page 4386, text. Additionally, the Bøgesø reference is silent with respect to any other salt of compound 38, much less a succinate or malonate salt thereof. Because of the foregoing, the Bøgesø reference teaches away from the succinate and malonate salts of Compound I of amended claim 47.

Consequently, the Bøgesø reference fails to teach, much less suggest or motivate, one of ordinary skill in the art to modify its teachings of the fumarate and maleate salts of compound 38 so as to achieve the succinate and malonate salts of Compound I of the present invention.

Furthermore, EP'073 cannot correct the deficiencies of the Bøgesø reference. Although EP'073 generically teaches Compound 38 of the Bøgesø reference (*see e.g.*, paragraph **[0002]**) and various salts with which to make acid addition salts of the compounds of EP'073 (*see e.g.*, paragraph **[0023]**), EP'073 is silent on the succinate and malonate salt of Compound I of the present invention: EP'073 discloses generally some illustrative salts, including succinic, as mere possibilities for acid addition salts of its compounds. *Id.* However, EP'078 clearly discloses a preference for the maleate salt of Compound I (*see* "Compd. 10", page 9, lines 6-7), as well as the hemifumarate, dimaleate, dihydrochloride, dioxalate, fumarate, and oxalate salts of related derivatives (*see e.g.*, Example 2, and compounds listed in paragraphs **[0043]**, **[0045]**, **[0047]**, and **[0050]**).

In fact, by focusing its teachings on hemifumarate, dimaleate, dihydrochloride, dioxalate, fumarate, maleate and oxalate acid addition salts of its compounds while being silent regarding a preference for a succinic or malonate acid addition salt, EP'073 teaches away from the present invention because as a result it fails to provide one of ordinary skill in the art an apparent reason to combine the known elements of the Bøgesø reference (*i.e.*, the maleate and fumarate salts of Compound I having potent effects so as to have met the goal of being mixed antagonists) with the known elements of EP'073 (*i.e.*, the maleate salt of Compound I and the hemifumarate, dimaleate, dihydrochloride, dioxalate, fumarate, maleate and oxalate salts of its compounds) to achieve the succinate and malonate salts of Compound I of the present invention. Additionally, because of this focused teaching of the hemifumarate, dimaleate, dihydrochloride, dioxalate, fumarate, maleate and oxalate salts and this silence with respect to a preference for a succinic or malonate acid addition salt, EP'073 fails to suggest or motivate one of ordinary skill in the art to modify the known elements of the Bøgesø reference so as to achieve the succinate and malonate salts of Compound I of amended claim 47. Consequently, the present invention is unobvious over the Bøgesø reference in view of EP'073.

Furthermore, US'448 cannot correct the deficiencies of the Bøgesø reference or those of EP'073. Although US'448 generically teaches various salts with which to make acid addition salts of the compounds of US'448 (*see e.g.*, col. 32, lines 26-43), US'448 is silent on the succinate and malonate salt of Compound I of the present invention. US'448 discloses generally some illustrative salts, including succinic and malonic acids, as mere possibilities for acid addition salts of its compounds. *Id.* However, US'448 clearly discloses a preference for the dihydrochloride salt of its compounds (*see e.g.*, Examples 8, 9a-c, 11, and 15, and compounds in Tables 5-7), while also showing a preference for the hydrochloride salt (*see e.g.*, Example 10 and compound 18-051 of Table 5), oxalate salt (*see e.g.*, compound 17-066 of Table 5), dichloride salt (*see e.g.*, compound Lu17-074 of Table 5) and trihydrochloride salt (*see e.g.*, compound 95/179 I of Table 5). Yet, US'448 is silent with respect to a preference for a succinic or malonate acid addition salt.

And, though the Office asserts that US'448 lists "othe[r] dicarboxylic acids" as preferred, including malonic acid, the Office is respectfully mistaken with respect to the latter. For example, although US'448 lists some "[r]presentative salts which are included in [the] preferred

group" of acid addition salts (*see e.g.*, col. 32, lines 26-31), this preferred group does not include malonic acid (or succinic acid), but does include the overwhelmingly exemplified "hydrochlorides". *See e.g.*, col. 32, lines 30-35. Rather, in its disclosure, malonic acid and succinic acid are *generally* disclosed as other suitable acids that "*may* be employed *if desired*." *See e.g.*, col. 32, lines 35-42 (emphasis added). At best, this disclosure is a mere invitation to try. But there is no reason to accept this invitation since the fumarate and maleate salts of the Bøgesø reference have the desirable mixed profile (D_1, D_2, 5-HT_2 and α_1) together with potent D1 activity, as previously discussed.

Without a doubt, by focusing its teachings on hydrochlorides acid addition salts of its compounds, while being silent regarding a preference for a succinic or malonate acid addition salt, US'448 teaches away from the present invention because as a result it fails to provide one of ordinary skill in the art an apparent reason to combine the known elements of the Bøgesø reference (*i.e.*, the maleate and fumarate salts of Compound I having potent effects so as to have met the goal of being mixed antagonists) with the known elements of US'448 (*i.e.*, hydrochlorides salts of is compounds) to achieve the succinate and malonate acid addition salts of Compound I of the present invention. Additionally, because of this focused teaching for hydrochlorides salts and silence with respect to a preferred succinate or malonate salt of its compounds, US'448 fails to suggest or motivate one of ordinary skill in the art to modify the known elements of the Bøgesø reference so as to achieve the succinate and malonate salts of Compound I of amended claim 47. Consequently, the present invention is unobvious over the Bøgesø reference and/or EP'073 in view of US'448.

Additionally, only with hindsight and use of Applicant's own specification as a blueprint, would one of ordinary skill in the art be motivated to modify the Bøgesø reference and/or EP'073 to achieve specifically the succinate and malonate salts of Compound I of amended claim 1. However, this is improper since using hindsight in finding the claimed invention obvious over prior art is impermissible. *See e.g.*, *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), at 22 (stating expressly that hindsight analysis of a patent challenged for obviousness is still to be avoided). Also, the Office's conclusion that because EP'073 and US'488 disclose a variety of "well-known" pharmaceutically acceptable salts as possibilities for acid addition salts of their respective compounds, it would have been obvious in view of the

Bøgesø reference for one skilled in the art to specifically select succinic acid and malonic acid from the prior art's general disclosure so as to arrive at the present invention is respectfully mistaken. As previously stated, both EP'073 and US'488 fail to provide an apparent reason, much less sufficient guidance, for selecting the succinic or malonic acid so as to modify the "goal-achieving" fumarate and maleate salts of the Bøgesø reference. Thus, it is only with hindsight that such a conclusion is made. Thus, the succinate and malonate salts of Compound I of amended claim 47 are not obvious in view of the combined references.

Furthermore, the succinate and malonate salts of Compound I of amended claim 47 are not obvious, because a determination of obviousness of a compound rests on more than its structure. "From the standpoint of patent law, a compound and all of its properties are inseparable." *In re Papesch* (315 F.2d 381, 391 (C.C.P.A. 1963). Additionally, Applicants respectfully disagree with the Office that the comparative evidence of the succinate, malonate and fumarate salts of Compound I in the specification is not persuasive in establishing the nonobviousness of the succinate and malonate salts. *See* Office Action, page 7. Evidence of a difference between the claimed compound and the prior art may take the form of "a comparison of test data showing that the claimed compositions possess unexpectedly improved properties...that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument or presentation of evidence that is pertinent." *See e.g., In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990)(*en banc* endorsement of *In re Papesch*); *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997)(citing *In re Dillon*). Further, whether a difference is "'striking' depends, not alone on the numerical ratio of the quantified value of the property being compared, but on the significance of that difference", such as whether the difference is of "any practical advantage". *In re D'Ancicco*, 439 F.2d 1244, 1248 (C.C.P.A. 1971).

Accordingly, even though the succinate and malonate salts of Compound I of the present invention are directed to comparable uses based on similar activity profiles as that of the combined references, the present salts unmistakably are not obvious because it would be clear to one skilled in the pharmaceutical arts that the 'striking' differences in the present invention salts compared to the prior art fumarate salt of Compound I have practical advantages. For example, (1) the increased aqueous solubility of both present invention salts compared to the fumarate salt

(*see e.g.*, Example 18 and Table 1; ~10x increase) clearly is advantageous, *e.g.*, with respect to a pharmaceutical product, and (2) the increased stability of both present invention salts compared to the prior art fumarate salt (*see e.g.*, Example 19 and Table 2; @ 60°C/80% RH) is advantageous, *e.g.*, for a pharmaceutical product. Also, with respect to the succinate salt, the lack of any degradation under light, very stressed conditions and more normal conditions compared to the prior art fumarate salt would be an apparent practical advantage, *e.g.*, with respect to a pharmaceutical product. *Id.*

Consequently, the comparative showing in the specification is persuasive in that the succinate and malonate salts of Compound I are not obvious in view of the combined references.

Furthermore, even without the comparative data, the salts of the present invention are not obvious because as discussed previously, it is very evident that the combined references are quite deficient such that there is no motivation therein to make what may appear to be an obvious change. *See In re Dillon, supra.*

Also, the Office offers that the *Pfizer v. Apotex* decision, 480 F.3d 1348 (Fed. Cir. 2007), is pertinent to its finding that the present invention obvious. *See* Office Action, pp. 7-8. But, the Office is respectfully mistaken. Although the recent *Pfizer v. Apotex* case dealt with the patentability of a particular salt form of an old compound, it is not controlling precedent with respect to patentability in the chemical and pharmaceutical arts. As it was not an *en banc* decision it does not over rule well established precedent. Applicants respectfully submit that *In re Papesch* (315 F.2d 381 (C.C.P.A. 1963), *supra*, is the well established precedent of the Federal Circuit in the chemical and pharmaceutical arts, and specifically with respect to determining obviousness.

Further, Applicants note that the *Pfizer v. Apotex* decision was a two member majority with the third member concurring in result only, and that there were three dissenting opinions in the Federal Circuit's denial to grant rehearing *en banc*, each dissenting opinion concerned that the two member majority erred in its legal determinations, which will confuse patent law with respect to obviousness. *See supra, Pfizer v. Apotex, reh'g en banc denied,* 488 F.3d 1377 (2007), *cert. denied* 128 S. Ct. 110 (2007) In fact, a concern of the dissents is with the very Pfizer Court conclusion that the Office relies upon in finding the decision of pertinence – namely, that salt in

question was the result of routine experimentation and thus obvious. This conclusion is in error, as two dissents highlight, because it contradicts the statutory requirement that "[p]atentability will not be negatived by the manner in which it was made." *See* 35 U.S.C. § 103(a); see also, *Pfizer v. Apotex, reh'g en banc denied, supra,* (J. Lourie and J. Rader, dissenting opinions)(quoting the statutory requirement of 35 U.S.C. § 103(a)).

Moreover, Applicants respectfully remind the Office that "[e]very case...raising the issue of obviousness...must be decided upon its own facts." *In re Jones,* 958 F.2d 347, 350 (Fed. Cir. 1992); *see also, In re Mayne,* 104 F.3d 1339, 1341 (Fed. Cir. 1997).

Therefore, and for the previous reasons, *Pfizer v. Apotex* is not pertinent to the patentability of the present invention and the salts of the present invention are not obvious.

In stating its position that the comparative evidence in the specification is unpersuasive, the Office notes that all the examples show a salt ratio of 1:1, and alleges that the claims cover other proportions. The Office is respectively mistaken. The specification plainly provides that the hydrogen succinate salt of Compound I refers to the 1:1 salt of Compound I and succinic acid, and similarly, hydrogen malonate salt of Compound I refers to the 1:1 salt of Compound I and malonic acid. *See* page 4, lines 8-12. Clearly, then, the comparative evidence of the examples supports the salts that are claimed.

For the foregoing reasons, amended claims 48, 50-54, 56-59 and 61-53, are patentably distinguishable over the combined references because of their dependency from amended claim 47. Claims 49, 55 and 60 have been canceled, therefore, the obviousness rejection with respect to these claims is moot.

Consequently, amended claims 48, 50-54, 56-59 and 61-53 are not obvious in view of the combined references. Applicants respectfully request the § 103(a) rejection be withdrawn.

D. SIDS reference

The Office noted that a copy of the disclosed Cox reference "is not seen in the file" and "[a] copy is needed for consideration." *See* page 8 of the Office Action. Because of an inadvertent error of Applicants with respect to the 2/21/08 SIDS that disclosed the Cox

reference, Applicants respectfully request the Office to confirm whether or not it deems a copy of the Cox is needed for consideration.

Applicants make this request since they now have found that the citation for the Cox reference on the SB08 Form of 2/21/08 inadvertently included the phrase, "P.6 of 512", which refers to the page of the specification of related USSN 11/816,383 where the Cox reference is disclosed. The full Cox reference, therefore, was being disclosed, not, *e.g.*, only page 6, as it may have appeared. Also, Applicants statement in connection with the 2/21/08 SIDS provided that a copy of the Cox reference was not being provided because of its voluminous nature. The Cox reference ("Preparative Enantioselective Chromatography", Oxford, UK: Blackwell Publishing LTD. 2005) is a 344 page book. However, as also stated on 2/21/08, Applicants will make all reasonable efforts to provide a copy of the book if the Office deems a copy is needed.

Applicants thank the Office for confirmation in view of the foregoing.

E. Conclusion

Applicants believe the claims are in condition for allowance, and earnestly solicit an early Notice of Allowance. Applicants invite the Examiner to contact the undersigned below if deemed helpful in advancing prosecution of the instant application.

Also, authorization is given to charge the Petition for Extension of Time and any additional fee, as well as credit any overpayment, to Deposit Account Number 50-3201.

Respectfully submitted,

/Margaret M. Buck, Reg. No. 54,010/
Margaret M. Buck
Registration No. 54,010

Lundbeck Research USA, Inc.
215 College Road
Paramus, New Jersey 07652
(201) 350-0781 (phone)
(201) 225-9571 (fax)